Letter to the Editor

Bilirubin Standardization in the Netherlands: Alignment within and between Manufacturers

To the Editor:

In 2008, two manufacturers lowered the values of their bilirubin calibrators: Abbott Laboratories by 18% and Roche by 10%–17% (different values per instrument). Beckman Coulter, Siemens/Bayer, and Siemens/Dade Behring did not restandardize their methods. In 2009, the Dutch External Quality Assessment Organization in Medical Laboratories [Stichting Kwaliteitsbewaking Medische Laboratoria (SKML)] investigated the impact on the mean measured concentration and the interlaboratory variation of assays for total bilirubin.

Pooled human serum was supplemented with unconjugated bilirubin (98%; Sigma–Aldrich). Serum samples were dispensed, frozen below −70 °C, and shipped on dry ice to the participating laboratories in the regular external quality-assessment program of February 2009. Mean target values were 26.7 µmol/L (95% CI, 26.1–27.3 µmol/L) and 68.7 µmol/L (95% CI, 67.2–70.21.5 µmol/L), as assigned with the Doumas reference measurement procedure (1–3) in the Joint Committee for Traceability in Laboratory Medicine (JCTLM)-listed reference laboratory in Hanover, Germany. The manufacturers also analyzed the samples in house with their respective routine methods. This design allowed a direct comparison of the results from routine laboratories and manufacturers’ in-house results with the target values assigned by the reference method.

Fig. 1 shows the results submitted by 183 routine laboratories, of which 99 laboratories used a Roche method, 42 used a Beckman Coulter method, 19 used an Abbott method, 9 used an Ortho Clinical Diagnostics VITROS method, 7 used a Siemens/Dade Behring method, and 7 used a Siemens/Bayer method. The Beckman Coulter group included users of the LX20, Synchro, and UniCel DxC 800 instruments; the Abbott group included users of the Arosset and ARCHITECT instruments; and the Roche group included users of the Cobas Integra, Cobas 6000, Modular Analytics, and Hitachi instruments. Because we found no relationship between results and instrument type, we present the data by manufacturer. The interlaboratory CVs at the high bilirubin concentration were approximately 3-fold higher for the Abbott (11%) and Roche (8%) instruments than for the Beckman Coulter (3%), Siemens/Dade Behring (2%), and Siemens/Bayer (3%) instruments.

The mean recovery of the spiked unconjugated bilirubin (expressed as a percentage of the target set by the reference laboratory for the high bilirubin concentration, excluding in-house results of manufacturers) was 86% for the Ortho VITROS method, 102% for the Siemens/Dade Behring method, 106% for the Roche method, 108% for the Beckman Coulter method, 110% for the Abbott method, and 111% for the Siemens/Bayer method. For the Siemens/Dade Behring method, results from the routine laboratories and the manufacturer’s in-house result were close to the target value. For the Beckman Coulter and Siemens/Bayer methods, the manufacturer and customer results were close but clearly higher than the target
value. For the Roche and Abbott methods, the in-house results from the manufacturers were close to the target, but the peer group means of their customers were higher. For the Ortho VITROS method, the laboratories obtained lower values, and the manufacturer’s in-house result was somewhere between the target value and the customers’ values. We cannot exclude the possibility that some laboratories reported unconjugated bilirubin (“Bu”) and the sum of bilirubin mono- and diglucuronide (“Bc”), although we explicitly asked VITROS users to report total bilirubin (“TBIL”). We were unable to clarify the method used upon retrospective inquiry of VITROS users.

From the external quality-assessment survey performed in 2009, it appears that recalibration of total bilirubin was “in progress” for the Roche and Abbott methods, which caused undesirably high interlaboratory variation. Results for the Beckman Coulter and Siemens/Bayer methods were high, compared with the target value of the Doumas reference measurement procedure, suggesting that calibration traceability with the certified reference materials and/or value assignment by reference laboratories with listed reference measurement procedures (4), both available from the JCTLM, have not been achieved. From a clinical point of view, the effect of restandardization by −10% to −20% is not very dramatic at commonly observed “adult” bilirubin concentrations of 20–80 µmol/L; however, restandardization of total bilirubin will affect the clinical decision to start or stop treatment at concentrations usually seen in neonates (100–600 µmol/L), owing to the specific treatment thresholds or decision limits for phototherapy and blood-exchange transfusion (5).

We conclude that notwithstanding the appearance of European In Vitro Diagnostic Directive 98/79/EC in 1998 and the foundation of the JCTLM in 2002, standardization has not been achieved. In addition, standardization of total bilirubin is complex, because the measurand is not unequivocally defined and the matrix may contain a mixture of bilirubin species (unconjugated, mono- and diconjugated, albumin-bound), which pose additional challenges.

Finally, because bilirubin restandardization has clinical consequences for the treatment of jaundiced neonates, the Chemistry Section of the SKML, in close collaboration with Dutch neonatologists, specifically aims to focus in 2010 on the analytical and clinical performance of commutable high-concentration neonatal bilirubin samples.

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References

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